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Effect of vaccination with live or killed *Pasteurella haemolytica* on resistance to experimental bovine pneumonic pasteurellosis

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SUMMARY

Using 6- to 8-month-old beef calves, 3 experiments were conducted to compare the effect of vaccination with live or killed *Pasteurella haemolytica* on resistance to a transthoracic challenge exposure with the organism and to correlate serum antibody response with resistance. In each experiment, calves were vaccinated twice at 1-week intervals and were challenge exposed 21 days after the first inoculation. Lung lesions were evaluated by a system, such that higher scores indicated the more severe lesions. In each experiment, calves immunized with live *P haemolytica* had lower lesion scores than calves vaccinated with saline solution or bacterin. In 2 of the experiments, the differences were significant ($P < 0.05$). In all experiments, calves vaccinated parenterally with a commercial *P haemolytica*/*P multocida* bacterin or with a formalin-killed *P haemolytica* bacterin had lesion scores that were not significantly different ($P > 0.05$) than for control calves vaccinated with saline solution.

Live and killed bacterial preparations induced a significant serum antibody response to *P haemolytica* as measured by a quantitative fluorometric immunoassay. The antibody response to vaccination was not affected by preexisting titers to *P haemolytica*. Serum antibody titers were not consistently as high for calves vaccinated with bacterins as for calves vaccinated with live organisms.

Although high antibody titers correlated with low lesion scores when calves vaccinated with saline solution or live organisms were analyzed collectively, there was not a significant correlation between the 2 variables when calves, vaccinated with saline solution or with bacterin, were analyzed collectively. These data indicate that, although bacterins may induce a detectable serum antibody response, they do not induce protection against transthoracic challenge exposure to *P haemolytica*.

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Bovine pneumonic pasteurellosis (shipping fever) is an economically important disease to the livestock industry.[1] *Pasteurella haemolytica* biotype A serotype 1 is frequently isolated from the lungs of cattle that die of severe fibrinous pneumonia associated with the disease.[2] The pathogenesis of pneumonic pasteurellosis is thought to result from interactions among viruses, stress, and *P haemolytica* or, less frequently, *P multocida*.[3,4] Lesions resembling the natural disease can be experimentally reproduced by several methods using *P haemolytica* alone or in combination with bovine respiratory viruses.[5-10]

The use of *Pasteurella* bacterins has been of limited value in controlling pneumonic pasteurellosis.[11-18] In several field trials, administration of bacterins has not protected against disease or has caused enhancement of disease. Immunization of calves with an experimental bacterin in Freund's incomplete adjuvant often stimulates an antibody response to *P haemolytica* somatic antigens, as detected by the indirect bacterial agglutination assay.[5,10,19] Animals thus immunized, however, were more susceptible to experimental pneumonic pasteurellosis.[5,10] Immunization of calves with a potassium thiocyanate or sodium salicylate capsular extract of *P haemolytica* has been reported to induce protection against experimental challenge exposure to the organism.[20,21] An immune response to the thiocyanate extract was detected by an enzyme-linked immunosorbent assay.[22]

Aerosol or parenteral immunization with live *P haemolytica* markedly enhances resistance to experimental disease induced by transthoracic challenge exposure with the bacterium.[23-25] Resistance was associated with an intense serum antibody response to *P haemolytica* somatic antigens, as detected by a quantitative fluorometric immunoassay.[23,25]

The purpose of the present study was to compare the protection afforded by live and killed *P haemolytica* vaccines against experimental pneumonic pasteurellosis and to correlate serum antibody response after vaccination, as detected by a fluorometric procedure, with resistance to transthoracic challenge exposure.

Materials and Methods

Cattle—A total of 59 Hereford, Angus, Brangus, and Hereford-Angus crossbred, male and female weaned calves 5 to 8

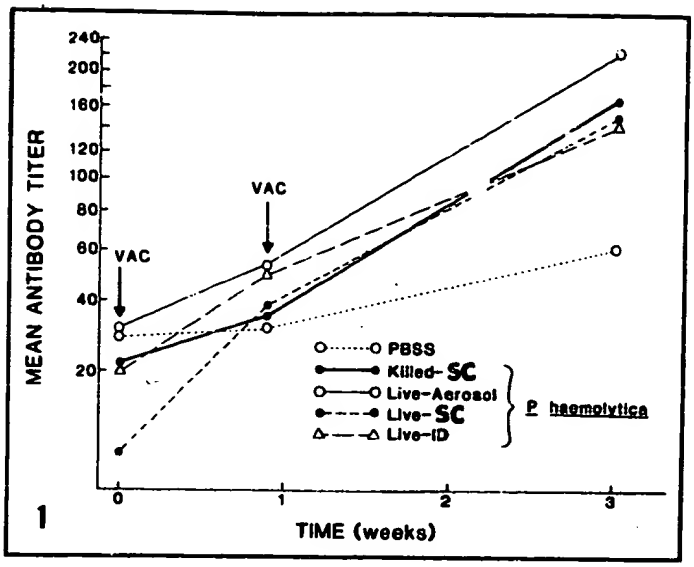

Fig 1—Experiment A: Antibody response to *P haemolytica* in calves vaccinated by various routes with live bacteria, a commercial bacterin, or PBSS. Each point represents the geometric mean titer of 2 or 4 samples. Vac = vaccinated.

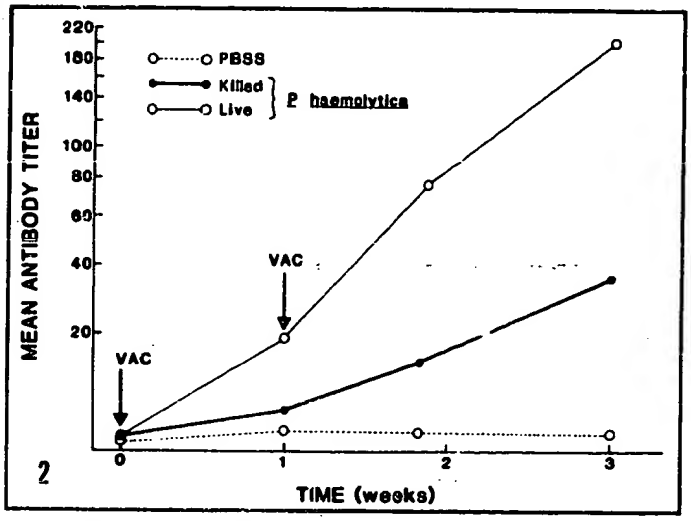

Fig 2—Experiment B: Antibody response to *P haemolytica* in calves vaccinated SC with live bacteria, a commercial bacterin, or PBSS. Each point represents the geometric mean titer of 6 or 7 samples. Vac = vaccinated.

months old, were obtained from closed herds and transported to holding pens where the experiments were conducted. Husbandry of the animals was as previously reported.[9]

Bacteriologic examination—The *P haemolytica* biotype A serotype 1 used in these experiments had been isolated originally from the trachea of a feedlot calf.[26] Vaccine and challenge cultures were grown on supplemented brain-heart infusion agar for 20 to 22 hours at 37 C in a 5% CO_2 environment as previously described.[9] Cultures were harvested in phosphate-buffered saline solution (PBSS, 0.01*M*, pH 7.4) at an approximate concentration of 10^9 colony-forming units (CFU)/ml, as determined photometrically. Actual CFU/ml were determined on each culture, using a spot-plate counting technique.

Serologic evaluation—Sera were tested for antibodies to *P haemolytica* by a quantitative fluorometric immunoassay (FIAX)[a] as previously described.[27] Antigen for the FIAX was a formalin-killed *P haemolytica* serotype 1 obtained from a 22-hour culture.

[a] International Diagnostic Technology Co, Santa Clara, Calif.

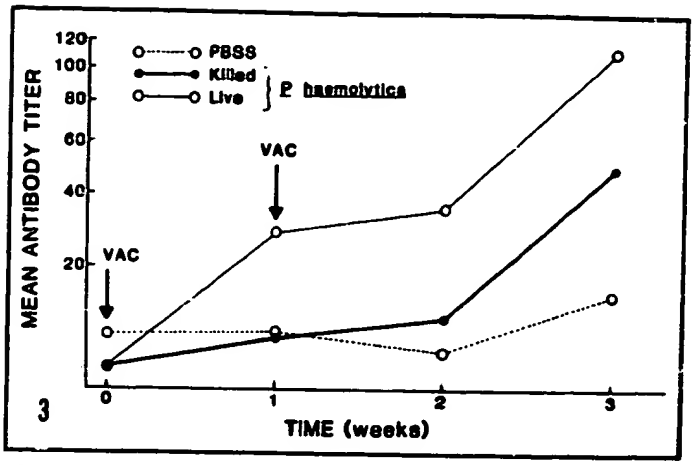

Fig 3—Experiment C; Antibody response to *P haemolytica* in calves vaccinated ID with live or formalin-killed bacteria or PBSS. Each point represents the geometric mean titer of 6 or 8 samples. Vac = vaccinated.

Titer equivalents were calculated for each sample by comparison to a standard curve constructed with sera of known endpoint titers.

Experimental design—Three experiments were conducted. Experiment A consisted of 5 groups of calves. Data from 4 of these groups has been reported previously.[25] Group 1 consisted of 4 calves that were aerosol or subcutaneously (SC) vaccinated with PBSS. Group 2 consisted of 4 calves that were given two, 2-ml SC injections of commercial *P haemolytica/P multocida* bacterin in alhydrogel at 1-week intervals. The bacterin was used 6 months before the expiration date listed for the product. Group 3 consisted of 2 calves that were aerosol vaccinated twice at 1-week intervals with live *P haemolytica* (approx 4×10^{10} CFU/exposure) as previously described.[24,25] Groups 4 and 5 each contained 4 calves that were given two, 5-ml injections of live *P haemolytica* (approx 10^9 CFU/ml) SC or intradermally (ID) at 1-week intervals as previously described.[25] Sera were obtained on days 0, 5, and 21 of the experiment.

Experiment B consisted of 3 groups. Group 1 consisted of 6 calves given two, 5-ml SC injections of PBSS at 1-week intervals. Group 2 consisted of 7 calves given two, 2-ml SC injections of a commercial *P haemolytica/P multocida* bacterin in alhydrogel at 1-week intervals. The bacterin was used 6 months before the expiration date listed for the product. Group 3 consisted of 6 calves inoculated SC with live *P haemolytica*, as described for group 3 in experiment A. Sera were obtained on days 0, 7, 12, and 21 of the experiment.

Experiment C was designed to determine whether the *P haemolytica* isolate could induce a protective immunity when injected in a live or in a killed state. An experimental *P haemolytica* bacterin was prepared in a 0.3% formalinized PBSS as previously described.[19] For injection, the killed organisms were washed twice in PBSS and adsorbed onto aluminum hydroxide in gel at a concentration equivalent to 10^9 CFU/ml, as determined photometrically. Group 1 consisted of 6 calves given two, 5-ml injections of PBSS intradermally at 1-week intervals. Group 2 had 8 calves given two, 5-ml ID injections of experimental bacterin at 1-week intervals. Group 3 had 8 calves given two, 5-ml ID injections of live *P haemolytica* (10^9 CFU/ml), as previously described.[25] Sera were obtained on days 0, 7, 14, and 21 of the experiment.

Twenty-one days after the first injection, all calves were transthoracically challenge exposed in each caudal lung lobe with a 5-ml volume of live organisms (actual concentration was from 0.6 to 1.1 $\times$ 10^9 CFU/ml) as previously described.[9] Four days later, calves were slaughtered, and lesions in the caudal lung lobes were evaluated by a lesion scoring technique previously described[25]: Scores of 0 to 20 were based on size and spread

TABLE 1—Serum antibody titers to *P haemolytica* in cattle vaccinated with the live or killed organisms

Experiment	Vaccine	Route	No. of cattle	Mean lesion (score ± SD)	Geometric mean antibody titer to *P haemolytica*		Linear regression analysis of antibody titer and lesion score		
					Day 0	Day 21	Correlation coefficient	*df*	Significance
A	PBSS		4	8.6 ± 6.0	29.6 ± 16.4	62.3 ± 29.7			
	Bacterin*	SC	4	7.0 ± 4.2	21.3 ± 12.4	171.2 ± 24.5	−0.601‡	6	$P > 0.10$
	Live	Aerosol	2	4.3 ± 1.1	33.9 ± 2.6	259.8 ± 17.6			
		SC	4	2.6 ± 2.8	5.1 ± 3.2	152.3 ± 17.4			
		ID	4	2.0 ± 2.4	20.9 ± 14.2	151.3 ± 9.9	−0.772§	12	$P < 0.01$
B	PBSS		6	13.8 ± 5.1	0.4 ± 4.1	1.4 ± 4.7			
	Bacterin*	SC	7	12.6 ± 5.6	1.1 ± 3.2	37.0 ± 5.26	0.120‡	11	$P > 0.30$
	Live	SC	6	2.9 ± 2.1	1.4 ± 2.7	212.6 ± 1.2	−0.692§	10	$P < 0.02$
C	PBSS		6	14.8 ± 6.3	7.4 ± 1.9	14.3 ± 1.6			
	Bacterin†	ID	8	14.4 ± 5.3	2.6 ± 3.0	49.2 ± 1.9	−0.0930‡	12	$P > 0.30$
	Live	ID	8	2.2 ± 1.4	2.5 ± 3.2	112.1 ± 1.2	−0.7681§	12	$P < 0.01$

* = 2 ml of commercial *P haemolytica/P multocida* bacterin. † = 5 ml of formalin-killed *P haemolytica*-aluminum hydroxide as adjuvant. ‡ = Analysis performed with data from PBSS and bacterin groups. § = Analysis performed with data from PBSS and live vaccine groups.

of lesion, with the higher scores indicating the more severe lesions.

Statistical analysis—Differences in mean antibody responses and lesion scores were analyzed by a Student's *t* test.[28] Antibody titers were compared with lesion scores by linear regression analysis.

Results

In each of the 3 experiments, vaccination with live and killed vaccines resulted in significant increases ($P < 0.05$) in mean antibody titers between days 0 and 21 (Table 1). Mean antibody titers induced by either vaccine were also significantly greater ($P < 0.025$) than mean antibody titers for PBSS-vaccinated controls. In each experiment, the increase in antibody titers between days 0 and 7 was greater for calves vaccinated with live organisms than for calves vaccinated with bacterins (Fig 1 through 3). In experiments B and C, antibody titers on day 21 were significantly higher ($P < 0.025$) in sera from calves vaccinated with live vaccines than in sera from calves given bacterins (Table 1). In all experiments, vaccination with live organisms resulted in antibody titer values of ≥ 53. All 4 bacterin-vaccinated calves in experiment A had titer values of > 127 on day 21; mean antibody titers were not significantly different ($P > 0.05$) from those associated with live vaccines. In experiments B and C, the antibody responses for individual bacterin-vaccinated calves were 3 to 252 (experiment B) and 15 to 107 (experiment C).

The data were examined for a possible association between preexisting antibody titers to *P haemolytica* (day 0) and the subsequent antibody response to vaccination. In experiment A, antibody titer values on day 0 were 0 to 60. Vaccination with a live or killed vaccine resulted in at least a 2-fold increase in titers in individual calves by day 21, exclusive of the preexisting antibody titer. In experiment B, antibody titers on day 0 were 0 to 17. Calf 29 had the highest antibody titer on day 0, and, by day 21, after vaccination with a bacterin, the calf had developed a titer of 252 (highest in the group). In experiment C, antibody titers on day 0 were 0 to 23. The calves with the 2 highest titer values (16 and 23) on day 0 developed the highest antibody titers in their treatment groups after vaccination with the live or with the killed vaccine. Other than the 4 calves listed above, an apparent association was not observed between the titer values on day 0 and the intensity of the serum antibody response on day 21 in individual calves in these experiments.

In all experiments, mean lesion scores for calves vaccinated with a bacterin were not significantly different ($P > 0.05$) from lesion scores for those that were given PBSS. In experiments B and C, mean lesion scores for calves vaccinated with live organisms were significantly less ($P < 0.01$) than mean lesion scores for bacterin-treated calves. In experiment A, however, mean lesion scores for calves vaccinated with live organisms were apparently, but not statistically, different ($P = 0.07$) than mean lesion scores for bacterin-treated calves.

In all experiments, when antibody titers (day 21) and lesion scores from calves vaccinated with PBSS or with live organisms were analyzed collectively by linear regression analysis, there was a significant correlation between the 2 variables (Table 1; correlation coefficients = −0.772 to −0.692, $P < 0.02$). When data from calves vaccinated with PBSS or with a bacterin were analyzed collectively, a significant correlation was not observed between antibody titers and lesion scores (correlation coefficients = −0.6014 to 0.1197, $P > 0.10$).

Because of the variable immune response to bacterins in experiments B and C, lesion scores for bacterin-treated calves with titers of > 50 were compared with lesion scores for bacterin-treated calves with antibody titers of < 50 (Table 2). Although mean antibody titers for calves with titers of < 50 were significantly different ($P < 0.025$) than the mean antibody titers for calves with titers of > 50, there was no significant difference ($P > 0.33$) between corresponding lesion scores.

Discussion

In the present studies, vaccination of calves with *P haemolytica* bacterins did not induce substantial resistance against a transthoracic challenge with the organism. Resistance was not substantially enhanced after the administration of a commercial bacterin (experiments A and B) or of a bacterin produced in our laboratory (experiment C). The purpose of experiment C was to determine whether the protection afforded by our *P haemolytica* isolate when used as a live vaccine necessitated that the organism be injected in a viable state or whether vaccination with this isolate, even when killed, would induce resistance to chal-

TABLE 2—Comparison of antibody titers and lesion scores for calves vaccinated with bacterins

Experiment	Antibody titer range: < 50 Calf No.	Antibody titer	Lesion score	> 50 Calf No.	Antibody titer	Lesion score
A	NA	NA	NA	5	150	8.5
				6	168	1.5
				7	240	11.5
				8	127	6.5
Mean ± SD					171.2 ± 24.5	7.0 ± 4.2
B	25	6	9	28	142	14.0
	26	3	20	29	252	20.0
	27	11	5.5	30	142	9.0
				31	95	11.0
Mean ± SD		5.8 ± 1.9*	11.5 ± 7.6†		150.4 ± 1.6	13.5 ± 4.6
C	44	48	15	48	103	8.5
	45	28	20	49	107	14.0
	46	44	20	50	66	7.5
	47	15	20	51	51	20.0
Mean ± SD		30.7 ± 1.7‡	16.3 ± 4.8§		78.0 ± 1.4	12.5 ± 5.8

* = Significantly different ($P < 0.01$) from mean antibody titers > 50 in experiment B. † = Not significantly different ($P = 0.36$) from lesion scores for group with titers > 50 in experiment B. ‡ = Significantly different ($P < 0.025$) from mean antibody titers > 50 in experiment C. § = Not significantly different ($P = 0.33$) from mean lesion scores for group with titers > 50 in experiment C. NA = not applicable.

lenge exposure. Results from the experiment indicated the necessity for immunization with our isolate as a live organism, possibly because formalin killing of the organism may remove or destroy important antigens or that replication of the organism in the host is required for the production of protective immunity, perhaps against nonstructural or minor structural components of the organism.

The antibody titer equivalents to *P haemolytica* were consistently high (53 to 277) among calves immunized with live organisms, but were variable (3 to 252) in calves immunized with the bacterins. Eight of 19 (42%) bacterin-treated calves did not develop a titer as high as the lowest value (53) for calves vaccinated with the live organism. Previous serologic studies in sheep, however, indicate that aluminum hydroxide in gel alone may be a poor adjuvant when used in conjunction with a salicylate extract of *P haemolytica*.[29] Therefore, the variable serologic response may be the result of the adjuvant used in these bacterins.

With the exception of calf 6 (experiment A), the development of a high antibody titer induced by the bacterin was not associated with substantial resistance to challenge exposure. Calf 6, a calf with a low lesion score, had the highest preexisting antibody titer to *P haemolytica* (68) of all the calves at the time of initial immunization. Because calf 6 was approximately 8 months old, that titer was probably not due to passively acquired colostral antibody; the titer may have been induced by prior natural exposure to the live organism.[30,31] Prior natural exposure to *P haemolytica*, as determined serologically, has been reported to enhance resistance to transthoracic challenge exposure with the organism.[32] Hence, the low lesion score of calf 6 was most likely due to protection afforded by the immunity after natural exposure and was not the result of vaccination with the bacterin.

In the present study, nearly 60% of the bacterin-treated calves developed antibody titers that were as high or higher than those induced by live organisms. There was, however, no correlation between these antibody titers and resistance. Conversely, as demonstrated in the present study and in previous studies, there was a significant correlation between high antibody titers, as measured by the FIAX, and resistance to challenge exposure in calves vaccinated with live organisms.[23,25,32] This indicates that antibody titer to *P haemolytica*, as measured by the FIAX, does not necessarily measure antibody to a protective antigen or antigens and is not, in itself, a measure of protective immunity.[25] The protective immunity afforded by live vaccines may be associated instead with anticytotoxin, cell-mediated, or anticapsular immunity, which were not measured in these studies.[33] Bacterins, on the other hand, may be ineffective because they fail to induce an immune response, or because, when an immune response occurs, it is not of a protective nature.

Results of the present study differ from those previously reported concerning parenteral or intrabronchial immunization of 8-week-old dairy calves with formalinized *P haemolytica*.[5,10,19] In those studies, parenteral bacterins were prepared in Freund's incomplete adjuvant. Intratracheal challenge exposure with *P haemolytica*, 4 weeks after a single exposure to that vaccine, resulted in enhanced disease. Further, serum antibody titers did not increase after vaccination of calves with preexisting serum antibody titers (> 1:20) to the organism, as detected by indirect bacterial agglutination.[19] In the present study, an increase in antibody titer was detected with the FIAX after vaccination, even in calves with preexisting titers. Because the FIAX correlates with indirect bacterial agglutination, this apparent discrepancy could be explained by the young age (8 weeks) of the calves in the previous study.[19] The preexisting antibody titers measured in the 8-week-old calves could have been passively acquired; our cattle (6 to 8 months of age) most likely had serum antibody from natural exposure. Passively acquired antibody could block a primary immune response, whereas the vaccination in the present study could have induced an anamnestic response. Because of the overall differences between the experimental designs (ie, ages and breeds of cattle, adjuvants, numbers of vaccinations, and challenge methods used), the results of the present and past studies[19] should not be compared. Both studies, however, indicated that *P haemolytica* bacterins do not protect cattle against experimental pneumonic pasteurellosis.

Because immunization with live *P haemolytica* enhances resistance to experimental challenge exposure and bacterins do not, several considerations must be made if effective killed products of *P haemolytica* are to be developed in the future. First, consideration of the protective antigens must be given. Potassium thiocyanate and sodium salicylate extracts of *P haemolytica*, presumably containing capsular material, afford protection against experimental pneumonic pasteurellosis in calves and lambs.[20,21,34] Aerosol immunization with live *P haemolytica* from young encapsulated cultures has been reported to afford slightly better protection against experimental transthoracic challenge exposure than did aerosol immunization with older nonencapsulated cultures.[29] Therefore, the function of capsular antigens in affording protection against pneumonic pasteurellosis needs further study. Second, the choice of adjuvant may be critical in determining the quantity and quality of the immune response that develops to *P haemolytica* antigens. Studies

with rodents indicate a marked difference in the ability of different adjuvants to stimulate humoral or cell-mediated immune responses.[35,36] Marked differences in the serologic responses of lambs vaccinated with capsular material of *P haemolytica* combined with different adjuvants has been reported.[29] Recently, vaccination with a *P haemolytica* bacterin in an oil adjuvant enhanced resistance to a bovine herpesvirus-1/*P haemolytica* challenge exposure, whereas vaccination with a bacterin adsorbed to aluminum hydroxide in gel did not enhance resistance.[b] Whether protective antigens are protein or carbohydrate in nature may determine which adjuvant is best to use. Third, because in vitro studies indicated that opsonization of bacteria may enhance cytotoxicity of the organism for macrophages, Wilkie[37] hypothesized that immune resistance may need to be aimed at production of cytotoxin neutralizing antibodies, rather than opsonizing antibodies. Studies using sera collected at necropsy indicated that cattle that died of fibrinous pneumonia had lower indirect bacterial agglutination titers to *P haemolytica* and lower cytotoxin neutralizing capacity than sera from cattle that died of other causes.[33,38] Cattle, which had been immunized with live *P haemolytica* or which had previous natural exposure to the organisms, had higher cytotoxin neutralizing titers in serum and were more resistant to challenge exposure than cattle that had been given bacterins or PBSS.[c] Therefore, the development of immunogens that stimulate protective immunity may be dependent on stimulation of an immune response to the cytotoxin of *P haemolytica*.

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Effect of vaccination **with live or killed** Pasteurella haemolytica **on resistance to experimental bovine pneumonic pasteurellosis.**

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Using 6- to 8-month-old beef calves, 3 experiments were conducted to compare the effect of vaccination with live or killed **Pasteurella haemolytica** on resistance to a transthoracic challenge exposure with the organism and to correlate serum antibody response with resistance. In each experiment, calves were vaccinated twice at 1-week intervals and were challenge exposed 21 days after the first inoculation. Lung lesions were evaluated by a system, such that higher scores indicated the more severe lesions. In each experiment, calves immunized with live P **haemolytica** had lower lesion scores than calves vaccinated with saline solution or bacterin. In 2 of the experiments, the differences were significant (P less than 0.05). In all experiments, calves vaccinated parenterally with a commercial P **haemolytica** /P multocida bacterin or with a formalin-killed P **haemolytica** bacterin had lesion scores that were not significantly different (P greater than 0.05) than for control calves vaccinated with saline solution. Live and killed bacterial preparations induced a significant serum antibody response to P **haemolytica** as measured by a quantitative fluorometric immunoassay. The antibody response to vaccination was not affected by preexisting titers to P **haemolytica** . Serum antibody titers were not consistently as high for calves vaccinated with bacterins as for calves vaccinated with live organisms. Although high antibody titers correlated with low lesion scores when calves vaccinated with saline solution or live organisms were analyzed collectively, there was not a significant correlation between the 2 variables when calves, vaccinated with saline solution or with bacterin, were analyzed collectively. These data indicate that, although bacterins may induce a detectable serum antibody response, they do not induce protection against transthoracic challenge exposure to P **haemolytica** .